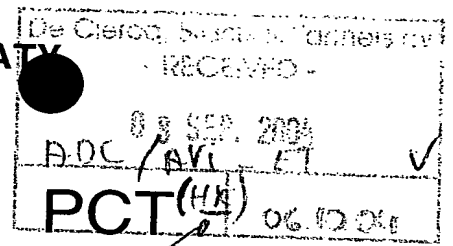


PATENT COOPERATION TREATY



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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WRITTEN OPINION (PCT Rule 66)

Date of mailing
(day/month/year) 06.09.2004

Applicant's or agent's file reference
ALGO-002-PCT1

REPLY DUE within 1 month(s)
from the above date of mailing

International application No.
PCT/EP 03/06049

International filing date (day/month/year)
10.06.2003

Priority date (day/month/year)
10.06.2002

International Patent Classification (IPC) or both national classification and IPC
G06F19/00

Applicant
ALGONOMICS N.V. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☐ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 10.10.2004

Name and mailing address of the international preliminary examining authority:



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I. Basis of the opinion

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, Pages

1-46 as originally filed

Claims, Numbers

1-46 as originally filed

Drawings, Sheets

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

Re Item I

Basis of the report

The basis of this written opinion is the application as originally filed. Reference is made to the following documents cited in the international search report:

D1: WO 98/59244 A

D2: KNEGTEL RONALD M A ET AL: "Molecular docking to ensembles of protein structures." JOURNAL OF MOLECULAR BIOLOGY, vol. 266, no. 2, 1997, pages 424-440, XP002944096 ISSN: 0022-2836

D3: MARELIUS JOHN ET AL: "Sensitivity of an empirical affinity scoring function to changes in receptor-ligand complex conformations." EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 14, no. 1, August 2001 (2001-08), pages 87-95, XP002227633 ISSN: 0928-0987

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- a. No opinion will be established with regard to novelty, inventive step, and industrial applicability because of the following clarity objections (Article 6 PCT).
- b. Although claims 1,16, and 44 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.
- c. Hence, independent claims 1,16, and 44 do not meet the requirements of Article 6 PCT and therefore no opinion will be given with regard to novelty, inventive step, and industrial applicability.
- d. However, to assist the applicant in filing a new set of claims and also with a view to the requirements of Article 33(1)-(5) PCT, an assessment of prior art has been

made.

- e. According to the description and in so far as it can be understood, it appears that the present application is directed to a method for predicting the binding affinity of a peptide for a MHC molecule, whereby an ensemble of peptide/MHC complexes is modelled by peptide backbone and side chain conformational modifications and the binding affinity of each peptide is evaluated.
- f. Document D1, cited by the applicant as prior art and which is provisionally considered to represent the closest prior art, discloses a system for predicting the binding affinity of a peptide to a MHC class molecule, by modelling all possible backbone structures for the peptide and then, for each backbone, modelling each possible side-chain conformation (see page 4, line 27 to page 5, line 2 and page 8, line 36 to page 9, line 9) and computing an affinity score for each peptide/molecule structure.
- g. In D1, the features of the present application whereby the binding properties are evaluated by calculating the potential energy of each complex and the conformational entropy of the complete ensemble are not present.
- h. Therefore D1 has the problem that its binding affinity calculation is not optimally accurate when input data is scarce and does not optimally separate between binding and non-binding peptides (the 'false-positive' problem).
- i. The problem of the closest prior art, as represented by D1, is solved by the system of the present application in that the present application ensures a greater accuracy because it bases the calculation of binding affinity on both potential energy terms and conformational entropy terms and it computes the term for conformational entropy from the ensemble of structures, rather than from individual complexes in the ensemble.
- j. Document ^{D2}~~D1~~ discloses a molecular docking method which uses ensembles of molecule conformations, in order to allow for conformational flexibility and because the ensemble provides for a better and more complete representation when input data is scarce or badly defined (see page 425, lines 32 to 60). Therefore D2 proposes a solution to the problem of D1 which is equivalent to the solution of the present application. It would be obvious and well within the customary practice followed by the person skilled in the related art to combine D1

and D2 to arrive at the subject matter of the present application.

- k. For the sake of completeness, it is pointed out that document D3 also discloses using ensembles of conformational structures to get an optimal calculation of binding affinities and could therefore be combined with D1 to arrive at the subject matter of the present application.
- l. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 43(2)(b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report.
- m. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.
- n. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion.
- o. Independent claims should be in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would be appropriate, with those features known in combination from the prior art (document D1) being placed in the preamble (Rule 6.3(b)(i) PCT) and with the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).
- p. If, however, the applicant is of the opinion that the two-part form would be inappropriate, then reasons therefore should be provided in the letter of reply. In addition, the applicant should ensure that it is clear from the description which features of the subject matter of the independent claims are already known in combination from document D1 (see PCT Guidelines, III-2.3a).